JOURNAL OF PSYCHOACTIVE DRUGS
https://doi.org/10.1080/02791072.2023.2190319

Taylor & Francis
Taylor & Francis Group

Psychedelic Treatments for Substance Use Disorder and Substance Misuse: A Mixed Methods Systematic Review

Raman Sharma MSc, Rachel Batchelor MSc, and Jacqueline Sin PhD

School of Health and Psychological Sciences, City, University of London, England, London, UK

ABSTRACT

Renewed interest in psychedelic substances in the 21st century has seen the exploration of psychedelic treatments for various psychiatric disorders including substance use disorder (SUD). This review aimed to assess the effectiveness of psychedelic treatments for people with SUD and those falling below diagnostic thresholds (i.e. substance misuse). We systematically searched 11 databases, trial registries, and psychedelic organization websites for empirical studies examining adults undergoing psychedelic treatment for SUD or substance misuse, published in the English language, between 2000 and 2021. Seven studies investigating treatment using psilocybin, ibogaine, and ayahuasca, alone or adjunct with psychotherapy reported across 10 papers were included. Measures of abstinence, substance use, psychological and psychosocial outcomes, craving, and withdrawal reported positive results, however, this data was scarce among studies examining a wide range of addictions including opioid, nicotine, alcohol, cocaine and unspecified substance. The qualitative synthesis from three studies described subjective experience of psychedelic-assisted treatments enhanced self-awareness, insight, and confidence. At present, there is no sufficient research evidence to suggest effectiveness of any of the psychedelics on any specific substance use disorder or substance misuse. Further research using rigorous effectiveness evaluation methods with larger sample sizes and longer-term follow-up is required.

ARTICLE HISTORY
Received 16 April 2022
Revised 24 January 2023
Accepted 6 February 2023

KEYWORDS
Psychedelic; substance use disorder; psilocybin; ibogaine; lysergic acid diethylamide; ayahuasca

Introduction

Individuals living with substance use disorder (SUD) are at an increased risk of developing adverse physical health outcomes such as cardiovascular and hepatic diseases, blood-borne infections, and greater mortality than the general population (Degenhardt et al. 2018). They often also have comorbid mental illnesses such as anxiety and mood-related disorders (Maremmani et al. 2017). Poor health outcomes subsequently impair their ability to function in society and can result in a reduced quality of life and premature death (Chesney, Goodwin, and Fazel 2014; Pasareanu et al. 2015).

Current treatments for SUD include pharmacological maintenance therapies such as methadone and buprenorphine, however, these carry the risks of abuse, dependency, overdose, and physical side effects such as nausea, respiratory depression, and withdrawal (Whelan and Remski 2012). Psychotherapy for SUD and substance misuse include cognitive behavioral therapy (CBT) and motivational interviewing, however, these are associated with high relapse rates when implemented alone (Lappan, Brown, and Hendricks 2020; (2012)). The treatment approaches for this debilitating condition remained static for the past half-century, despite the low success rates (Pisano et al. 2017).

Psychedelic drugs are a class of psychoactive substances that can induce alterations of conscious states, as well as a variety of biological, cognitive, and emotional effects (Taylor 1971). Such effects gained interest for their therapeutic action, when administered within a therapeutic context (di Leo 1975). The reemergence of psychedelic medicine has once again sparked the question of its utility for treating mental disorders, including mood, anxiety, and substance-use disorders (dos Santos et al. 2018). In the recent decade, there have been a few literature reviews examining psychedelic treatments for SUD (DiVito and Leger 2020; dos Santos et al. 2018; Winkelman 2014). These reviews suggest that psychedelics such as psilocybin, lysergic acid diethylamide (LSD), ibogaine, and ayahuasca have qualitative evidence of potential effectiveness and usefulness in substance misuse treatment, hence could offer a novel alternative to existing treatments. There are also complex differences between various psychedelics and treatment approaches using psychedelics as mono- or adjunct therapy (most commonly with psychotherapy),

CONTACT Raman Sharma raman.sharma@city.ac.uk School of Health and Psychological Sciences, City, University of London, Myddelton Street Building, 1 Myddelton Street, England, London EC1R 1UW, UK

as well as the different SUDs under treatment (DiVito and Leger 2020; dos Santos et al. 2018).

Of all psychedelic drugs, psilocybin reportedly has the most favorable safety profile and has demonstrated low physiological toxicity, non-addictive effects, and no associated persisting adverse effects during or after use (Lowe et al. 2021). Psilocybin is a psychoactive alkaloid contained in over 100 species of hallucinogenic mushrooms (De Veen et al. 2017). Once ingested, psilocybin is metabolized to psilocin, which exerts its effect on 5-HT2A and other serotonin receptors, and these mediate the hallucinogenic, anti-depressant, and anti-anxiety effects (Lowe et al. 2021; Mertens et al. 2020).

LSD is a semisynthetic serotonergic substance whose defining psychoactive properties (i.e. antidepressant and anxiolytic effects) are thought to be mediated primarily through serotonin type 2A receptor agonism (Dos Santos et al. 2016). Acute LSD ingestion produces an altered state of consciousness characterized by simulation of affect, introspection, and perceptual changes (Passie et al. 2008). The safety of LSD has been documented extensively and has not been found to produce physiological toxicity nor any reports of death from overdose (Garcia-Romeu, Kersgaard, and Addy 2016).

Ibogaine is a psychoactive indole alkaloid found in the African rainforest shrub *Tabernanthe iboga* root bark (Cloutier-Gill et al. 2016) which has affinity for a range of neurotransmitter systems (Mačiulaitis et al. 2008). Noribogaine, the active metabolite in ibogaine, exhibits similar receptor characteristics, however, has a high affinity for mu and kappa opioid receptors. Its complex receptor profile, in addition to its relatively long half-life, contributes to its effects in improving opioid withdrawal symptoms and decreasing opioid craving (Malcolm, Polanco, and Barsuglia 2018). Previous research on ibogaine for opioid detoxification reported positive effects in individuals' ability to cope with stress, and subjective feelings of inner peace, joy, and heightened spiritual awareness (Davis et al. 2018). However, Ibogaine has been banned in some countries due to safety concerns related to its cardiac effects (Cloutier-Gill et al. 2016).

Ayahuasca is a traditional Amazonian psychedelic plant compound consisting of a mixture of the vine *Banisteriopsis* caapi and the bush *Psychotria viridis*, which contain beta-carboline alkaloids and the hallucinogen N,N-dimethyltryptamine (DMT), respectively (dos Santos 2013). The beta-carboline alkaloids found in *B. caapi* make the DMT from *P. Viridis*. orally available (Winkelman 2014), which affects serotonin receptors and produces hallucinogenic effects. Acute ayahuasca ingestion induces a transient-modified state of awareness characterized by introspection, visions, and emotional memories (Soler et al. 2016) which may facilitate an enhanced sense of self-acceptance and self-awareness leading to resolved emotional trauma (Argento et al. 2019).

The current review aimed to systematically investigate contemporary studies on the clinical use of psychedelic substances as an independent treatment or adjunct with psychotherapy, for the treatment of SUD and substance misuse. Further objectives included: 1. To assess if psychedelic substances are effective for SUDs (current diagnosis), and treatment resistant SUD (history of unsuccessfully treated SUD); 2. To describe service users' perspectives of psychedelic treatment; and; 3. To identify the strengths and barriers to the clinical implementation of psychedelic treatments.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). We used the PICO (population, intervention, comparator, and outcome) framework to formulate the research question and its scope. The "population" of interest included adults aged 18–65 years old with either a diagnosis of SUD as classified by ICD (World Health Organization 2019) or The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2013) or a history of unsuccessfully treated substance misuse, as their primary problem. The "intervention" included medically prescribed and supervised psychedelic substances as defined by the Alcohol and Drug Foundation (Alcohol and Drug Foundation 2019). This included substances such as psilocybin, ayahuasca, LSD (including DMT), ibogaine, NBOMe, 2C-B (4-Bromo-2, 5-dimethoxyphenethylamine), and salvia, while excluding ketamine, 3,4-methylenedioxymethamphetamine, and mescaline. Where relevant, "comparators" included inactive controls such as treatment as usual and waitlist, or active controls which included prescribed psychotropic medication and any form of psychological therapies or psychoeducational intervention. The review's primary outcome was abstinence or substance use reduction. Secondary outcomes included measures of well-being, quality of life, craving, withdrawal symptoms, and subjective experiences.

To maximize usable data, we included all outcomes data measured with validated scales. For instance, for abstinence and substance use reduction, we included data measured with the 4-Week Substance Use Scale, Timeline Follow-back, or biological markers such as carbon monoxide and urine cotinine levels. For well-being or quality of life outcomes, Symptoms Checklist-

90 scale, McGill Quality of Life scale, Profile of Mood scale, or Beck Depression Inventory II or similar tools were considered. For craving and withdrawal, commonly used scales included Subjective Opiate Withdrawal Scale (SOWS); Clinical and Objective Withdrawal Scale (COWS and OOWS). Subjective experiences were reported through qualitative data such as interviews. A review protocol has been published in PROSPERO (Prospective Register of Systematic Reviews, CRD42021232944 Sharma and Sin 2021).

Eligibility criteria

Empirical studies using any study design were included. As long as SUD or substance misuse was the primary diagnosis of the participants in the studies, they were included regardless of the presence of other comorbid physical or mental health problems. Studies were excluded if there was insufficient or unclear information on treatment regimen using psychedelics (e.g. substance used, and dosage) or psychedelic-assisted psychotherapy (e.g. type of psychotherapy, duration, frequency), prohibiting reliable replication of treatment and rigorous assessment of study against eligibility criteria. No studies were excluded based on the route, dosage or regimen of drug administration and the settings under which the study was conducted.

Search strategy and information sources

Based on the PICO constructs, our search strategy consisted of the following key terms: (*substance use disorder OR (cannabis/alcohol/opioid/narcotic/cocaine/tobacco) adj1 (dependence/misuse)*) AND ((*psychedelic/hallucinogen/psilocybin/ibogaine/lysergic acid diethylamide/LSD/ayahuasca)* OR/adj1 (*psychotherapy*/psychodynamic/interpersonal/cognitive/behave*/mindfulness/meditation/ccounsel*/talking therap**) OR (*psychedelic assisted psychotherapy*)). *Psychedelic* and *hallucinogen* MeSH terms were included to encompass lesser known substances on the ADF Drug Wheel such as 2C-B, NBOMe, and salvia, and any other psychedelic substances. See Appendix A for an example of a full search strategy.

To search for papers reporting empirical studies published in English, from 1st January 2000 (the year of publication for the DSM-IV Text Revision) to 5th March 2021, we inputted and adapted the search strategy into eight databases: CINAHL (Cumulative Index to Nursing and Allied Health Literature), MEDLINE (Medical Literature Analysis and Retrieval System Online), PsychInfo (Psychological Information) via EBSCOhost, EMBASE (Exceptra Medica Database) and MEDLINE® via Ovid, the LILACS (Latin American & Caribbean Health Sciences Literature) database, CENTRAL (Cochrane Central Register of Controlled Trials) for reports of controlled trials, and Web of Science. Grey literature was also searched, through ProQuest and trial registry (www.clinicaltrials.gov), and the Multidisciplinary Association for Psychedelic Studies website. Once an initial set of papers from the databases were identified, we performed backward and forward searches in the reference lists and citations of the identified papers for any additional studies.

Study selection

EndNote X9.3.3 (Clarivate 2021) was used for all study selection processes. Once all items identified from the searches were inputted into the Endnote library, duplicates were removed. Titles and abstracts were initially screened and then full-text reports were screened against the eligibility criteria. One reviewer (RS) screened all items at all stages; a second reviewer (JS) carried out an independent random 20% sample check at each screening stage. Any disagreements were resolved through discussion.

Data extraction process

Relevant data from the included studies were extracted from a summary table. One reviewer (RS) conducted the data extraction and another (JS) independently checked the data extraction for accuracy and completeness. Extracted data included: 1. author of study, year of publication, and country; 2. study design; 3. sample size and participant characteristics including gender, mean age (SD), ethnicity; 4. substance of dependence; 5. Treatment including dosage, duration, and frequency of intervention; 6. Outcomes, measures used, and time points.

Quality assessment

The Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS) tool was used to assess the risk of bias of the included studies (Zingg et al. 2015). The tool consists of two parts: (1) a list of quality criteria specific for each study design and criteria applicable to all designs (e.g. ethics), using 3-point scales (2 points=criterion met, 0 points=criterion not met, 1 point=unclear if criterion is met) with the sum providing a total global quality score for the study; 2) a "decision matrix" which uses a study's score to assess its

robustness by measuring it against a minimum score requirement specified by the type of study design. For this review, we used the global quality score of included studies to note the quality of the studies rather than excluding them based on the minimum score requirement. This process was conducted independently by two reviewers (JS and RS). Discrepancies were resolved through seeking additional data and discussion until consensus was reached.

Synthesis methods

Data synthesis began with an overview of study characteristics and tabulation of the extracted data to scope treatment regimens using psychedelics solely or as an adjunct to psychotherapy, and the types of substance being misused or addicted to. A mixed methods synthesis involving a convergent segregated approach was conducted to synthesize the data across all studies (Lizarondo et al. 2020), focusing on pre-specified outcomes rather than specific psychedelic therapies (drugs/models) for particular substance of abuse for overall effectiveness in each area of interest. Meta-analysis was inappropriate given the heterogeneous data available. Instead, we carried out separate narrative syntheses of the quantitative and qualitative data to investigate psychedelic treatment effectiveness on various outcomes and participants' subjective experiences. We then performed a meta-synthesis using data across studies to contextualize the findings and recommendations (Joanna Briggs Institute 2014).

Results

Search procedures identified 4721 articles, 239 were excluded as duplicates. From 4482 titles screened, 4311 articles were excluded as they did not meet inclusion criteria. Abstract screening excluded another 126 articles, leaving 45 articles for full-text screening. Reasons for the exclusion of 35 papers included non-primary studies (21), ineligible population (2), or intervention (5), no usable outcome data (1), ongoing studies (4) and unable to access (2). A total of 10 articles reporting seven studies met all the eligibility criteria and were included (see Figure 1).

All included studies were published within the last decade. Two studies were conducted in the USA, two in Mexico, and one each in Canada, the West Indies, and New Zealand. Various psychedelic interventions for SUD and substance misuse were studied, namely psilocybin (Bogenschutz et al. 2015; Johnson et al. 2014), ibogaine including noribogaine (Brown and Alper 2018; Glue et al. 2016; Malcolm, Polanco, and Barsuglia 2018; Mash et al. 2018), and ayahuasca (Thomas et al. 2013). One paper by Argento et al. (2019) was used solely for demographic data extraction from the ayahuasca-assisted psychotherapy study. No studies were identified that examined LSD. See Table 1 for a summary of characteristics of included studies.

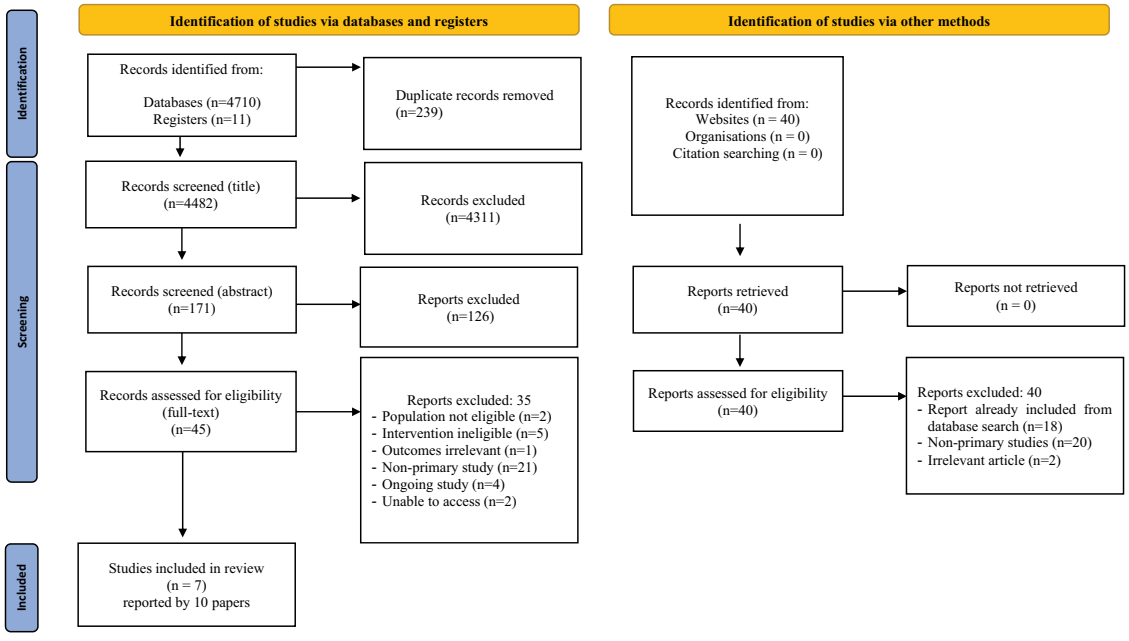

Figure 1. PRISMA flow diagram.

Table 1. Summary of included studies.

Author (year) Country	Study Design	Sample Size (*n*=): Female (F), Male (M) Mean age (SD) Ethnicity: %	Substance of Dependence	Duration of Treatment and Intervention	Outcomes (Measures) and Time Points
Bogenschutz et al. (2015)*; Nielson et al. (2018) USA	Before-and-after study	n = 10: 4F, 6 M 40.1 (10.3) Native American/Alaska Native: 20% African American: 10% Hispanic: 40% White: 30%	Alcohol	12-week program Psilocybin orally – 2 sessions 1st dose week 4 (*n* = 10) = 0.3 mg/kg, 2nd dose week 8 (*n* = 7) 0.4 mg/kg, and motivational enhancement therapy – 7 sessions	**Substance Use (Mean % Drinking Days)**: Decreased from~42% at baseline to~12% at Weeks 1–4 post first psilocybin session ($p = .009$), ~17% at Weeks 5–8 post first psilocybin session ($p = .015$), ~11% at Weeks 9–20 post first psilocybin session ($p = .006$), and~18% at Weeks 21–32 post first psilocybin session ($p = .007$). **Substance Use (Mean % Heavy Drinking Days)**: Decreased from~35% at baseline to~9% at Weeks 1–4 post first psilocybin session ($p = .007$), ~14% at Weeks 5–8 post first psilocybin session ($p = .019$), ~11% at Weeks 9–20 post first psilocybin session ($p = .010$), and~13% at Weeks 21–32 post first psilocybin session ($p = .004$). **Self-Efficacy to Abstain from Alcohol Use (Alcohol Abstinence Self-Efficacy)**: Temptation mean scores decreased from baseline (38.30) to 5-weeks post-psilocybin session (24.56) ($p < .05$) and 20-weeks post-psilocybin session (26.63) ($p < .05$). Confidence mean scores increased from baseline (40.10) to 1-week post-psilocybin session (55.56) ($p < .05$). **Consequences of Alcohol Use (Short Inventory of Problems)**: Interpersonal mean scores decreased from baseline (4.80) to 20-weeks post-psilocybin session (2.56) ($p < .01$) and 32-weeks post-psilocybin session (2.56) ($p < .01$). Intrapersonal mean scores decreased from baseline (7.30) to 20-weeks post-psilocybin session (3.89) ($p < .05$) and 32-weeks post psilocybin session (3.67) ($p < .05$). **Alcohol Craving (Penn Alcohol Craving Scale)**: Mean scores decreased from baseline (16.00) to 5-weeks post-psilocybin session (10.00) ($p < .01$), 8-weeks post-psilocybin session (12.11) ($p < .05$), and 32-weeks post-psilocybin session (8.11) ($p < .001$). **Mood (Profile of Mood Scale)**: Vigor mean scores increased from baseline (5.60) to 20-weeks post-psilocybin session (9.56) ($p < .05$). **Motivation (Stages of Change Readiness and Treatment Eagerness Scale)**: Ambivalence mean scores decreased from baseline (15.70) to 20-weeks post-psilocybin session (12.00) ($p < .05$) and 32-weeks post-psilocybin session (11.56) ($p < .05$). Taking Steps mean scores increased from baseline (32.30) to 1-week post-psilocybin session (36.33) ($p < .05$), 4-weeks post-psilocybin session (36.33) ($p < .01$), 5-weeks post-psilocybin session (37.33) ($p < .01$), 8-weeks post-psilocybin session (35.78) ($p < .05$), and 20-weeks post-psilocybin session (36.00) ($p < .05$). **2nd Report** Nielson et al. (2018) **Qualitative Content Analysis** (Day after each psilocybin session) • **Ego-dissolution**: Fear of completely losing sense of self, and taking comfort in retaining identity • **Relationship to alcohol**: Participants consistently described a change in their relationship to alcohol • **Motivation for change**: Expressions of desire to change and increased confidence in avoiding alcohol • **Commitment to change**: Participants discuss doing things differently and serving a purpose

(*Continued*)

Table 1. (Continued).

Author (year) Country	Study Design	Sample Size (*n*=): Female (F), Male (M) Mean age (SD) Ethnicity: %	Substance of Dependence	Duration of Treatment and Intervention	Outcomes (Measures) and Time Points
Brown and Alper (2018) Mexico	Case series	n = 30: 5F, 25 M 29 (9.0) White: 90% Hispanic: 3% Other: 6%	Opioid	3–6-day treatment Ibogaine HCl orally Total average dose 1540 ± 920 mg Test dose: 3 mg/kg Flood dose: 12 mg/kg (2–12 hours posttest dose) Booster dose: 3-5 mg/kg (1–16 hours post-flood dose)	**Abstinence (Opioid-free days in previous 30 days)**: 50% (*n* = 15) reported no opioid use in past 30 days at 1-month follow-up. 33% (*n* = 10) reported no opioid use in past 30 days at 3-month follow-up. 20% (*n* = 6) reported no opioid use in past 30 days at 6-month follow-up. 37% (*n* = 11) reported no opioid use in past 30 days at 9-month follow-up. 23% (*n* = 7) reported no opioid use in past 30 days at 12-month follow-up. **Withdrawal – Self-rated(SOWS1**) (*n* = 27): Mean scores decreased from pre-treatment baseline (31 points) to post-ibogaine treatment (14 points) ($p < .001$). Mean time between SOWS administration was 76.5 hours. **Composite Drug Use and Functioning Scale (Addiction Severity Index Composite)**: Drug Use composite scores decreased from baseline (0.40) to 1-month post-ibogaine treatment (0.11) ($p < .001$), 3-months post-ibogaine treatment (0.15) ($p < .001$), 6-months post-ibogaine treatment (0.12) ($p < .001$), 9-months post-ibogaine treatment (0.13) ($p < .001$), and 12-months post-ibogaine treatment (0.17) ($p < .001$). Alcohol Use composite scores increased from baseline (0.08) to 1-month post-ibogaine treatment (0.09)†, decreased from baseline to 3-months post-ibogaine treatment (0.07) †, and increased from baseline to 6-months post-ibogaine treatment (0.16) †, 9-months post-ibogaine treatment (0.12) †, and 12-months. post-ibogaine treatment (0.16) †. Family/Social Status composite scores decreased from baseline (0.24) to 1-month post-ibogaine treatment (0.07) ($p < .001$), 3-months post-ibogaine treatment (0.06) ($p < .001$), 6-months post-ibogaine treatment (0.08) ($p < .01$), 9-months post-ibogaine treatment (0.03) ($p < .001$), and 12-months post-ibogaine treatment (0.04) ($p < .001$). Employment Status composite scores increased from baseline (0.34) to 1-month post-ibogaine treatment (0.44) ($p < .01$), decreased from baseline to 3-months post-ibogaine treatment (0.33) † and 6-months post-ibogaine treatment (0.26) †, increased from baseline to 9-months post-ibogaine treatment (0.37) † and decreased from baseline to 12-months post-ibogaine treatment (0.25) †. Legal Status composite scores decreased from baseline (0.22) to 1-month post-ibogaine treatment (0.10) ($p < .01$), 3-months post-ibogaine treatment (0.04) ($p < .01$), 6-months post-ibogaine treatment (0.14) ($p < .05$), 9-months post-ibogaine treatment (0.05) ($p < .05$), and 12-months post-ibogaine treatment (0.10) ($p < .01$). Medical Status composite scores increased from baseline (0.19) to 1-month post-ibogaine treatment (0.26) †, 3-months post-ibogaine treatment (0.27) †, and 6-months post-ibogaine treatment (0.25) †, decreased from baseline to 9-months post-ibogaine treatment (0.15) †, and increased from baseline to 12-months post-ibogaine treatment (0.26). Psychiatric Status composite scores decreased from baseline (0.27) to 1-month post-ibogaine treatment (0.18) †, decreased from baseline to 3-months post-ibogaine treatment (0.17) ($p < .05$), 6-months post-ibogaine treatment (0.16) ($p < .01$), and decreased from baseline to 9-months post-ibogaine treatment (0.14) †, and 12-months post-ibogaine treatment (0.23) †.

(*Continued*)

Table 1. (Continued).

Author (year) Country	Study Design	Sample Size (*n*=): Female (F), Male (M) Mean age (SD) Ethnicity: %	Substance of Dependence	Duration of Treatment and Intervention	Outcomes (Measures) and Time Points
Glue et al. (2016) New Zealand	RCT	n = 27: 6F, 21 M 41.2 (not specified) White: 74% Maori: 19% Other: 7%	Patients on opioid substitution therapy (25-80 mg/day for at least 30 days prior to screening)	4-day treatment with Noribogaine orally (*n* = 18) 60 mg/120 mg/240 mg (*n* = 6 for each dose level) Placebo orally (*n* = 9) (*n* = 3 for each dose level)	**Withdrawal – Self and clinician rated (SOWS, COWS2, OOWS3)**: Increases in all scales 1–2 hours prior to resumption of opioid substitution therapy, and decreased within 1–3 hours of opioid substitution therapy. †. **Withdrawal – Pupil Diameter (mm)**: Mean pupil diameter increased by 0.47 mm in the 2 hours prior to resumption of opioid substitution therapy across Treatment Arms (Placebo, Noribogaine 60 mg, Noribogaine 120 mg, Noribogaine 180 mg) †. **Time (hours) to Resumption of Opioid Substitution Therapy (Mean (SD))**: - **By Treatment Arm**: **Placebo** (*n* = 9): 13.9 (7.4) **60 mg Noribogaine** (*n* = 6): 8.6 (3.7) †. **120 mg Noribogaine** (*n* = 6): 22.5 (10.3) †. **180 mg Noribogaine** (*n* = 6): 11.4 (5.0) †. - **By Cohort**: Placebo results for each cohort were similar to those of corresponding active arm (Pearson's *r* = 0.993) **Cohort 1**: Placebo (*n* = 3): 9.0 (3.1)/60 mg Noribogaine 8.6 (3.7) †. **Cohort 2**: Placebo (*n* = 3): 20.5 (9.6)/120 mg Noribogaine 22.5 (10.3) †. **Cohort 3**: Placebo (*n* = 3): 12.1 (3.3)/180 mg Noribogaine 11.4 (5.0) †.

(*Continued*)

Table 1. (Continued).

Author (year) Country	Study Design	Sample Size (*n*=): Female (F), Male (M) Mean age (SD) Ethnicity: %	Substance of Dependence	Duration of Treatment and Intervention	Outcomes (Measures) and Time Points
Johnson et al. (2014)*; Johnson, Garcia-Romeu, and Griffiths (2017) USA	Before-and-after study	n = 15: 5F, 10 M 51 (10.5) White: 93% Asian: 7%	Nicotine	15-week programme Psilocybin orally (2 doses weeks 5 (20 mg/70 kg), & 7 (30 mg/70 kg), and 1 optional high dose week 13) (*n* = 3) (30 mg/70 kg) and Cognitive Behavioral Therapy for smoking cessation (weeks 1–4 before psilocybin administration)	**Abstinence (Carbon Monoxide Levels, Urine Cotinine, Timeline Follow-back)**: 80% (*n* = 12/15) showed 7-day point prevalence abstinence at 6-month follow-up ($p < .001$). **Substance use (Timeline Follow-back)**: Mean cigarettes per day (CPD) decreased from intake (16.5) to 6-month follow-up (2.7) ($p < .001$). **Biological Markers (Breath Carbon Monoxide Levels and Urine Cotinine)**: Significant reductions in CO levels ($p < .01$) and urine cotinine ($p = .4$) from intake to 6-month follow-up. †† **Craving (Questionnaire of Smoking Urges)**: Significantly decreased from intake to 6-month follow-up ($p < .001$). ††. **Self-efficacy (Smoking Abstinence Self-efficacy Scale)**: Significant increase in confidence to abstain ($p < .001$) and significant decrease in temptation to smoke ($p < .001$) from intake to 6-month follow-up. †† **Withdrawal (Wisconsin Smoking Withdrawal Scale)**: Significant decrease from intake to 6-month follow-up ($p = .009$). †† **2nd report: Johnson, Romeu, and Griffiths (2017)** **Abstinence (Carbon Monoxide Levels, Urine Cotinine, Timeline Follow-back)**: 67% (*n* = 10/15) abstinent at 12-month follow-up, 90% abstinent at longer term (>16 months, mean interval of 30 months) follow-up ($p < .001$). **Substance Use (Timeline Follow-back)**: Significant decrease in Mean CPD from Intake (16.5 CPD) to 12-month follow-up (3.3 CPD) ($p < .001$) and 30-month follow-up (4.3 CPD) ($p < .001$). **Persisting Effects (Persisting Effects Questionnaire)**: Higher rates of positive effects than negative in all domains (Attitudes about Life and Self, Mood, Behavior Changes, Mood Changes, Relationships, and Spirituality) at 12-month follow-up. • **Positive Behavior Change** (**Mean)**: Increased from Session 1(52.9) to 12-month follow-up (64.0) †. • **Negative Behavior Change (Mean)**: Decreased from Session 1 (7.1) to 12-month follow-up (4.0) †. • **Positive Mood Change (Mean)**: Increased from Session 1 (34.6) to 12-month follow-up (53.0) †. • **Negative Mood Change (Mean)**: Decreased from Session 1 (14.1) to 12-month follow-up (7.0) †.
Malcolm, Polanco, and Barsuglia (2018) Mexico	Case series	n = 40: 15F, 25 M 31.28 (8.38) White: 77.5% Asian: 5% Other: 17.5%	Opioid use disorder	1-week treatment Ibogaine HCl orally 18-20 mg/kg. Test dose: 100 mg Flood dose: Remainder given within 2 hours Booster: 1-5 mg/kg given if post-acute withdrawal symptoms occur at 72-hours post-ibogaine administration 4 days in treatment center, 3 days in residential setting	**Withdrawal – Clinician-rated (COWS)**: Mean group scores decreased from 48-hours pre-ibogaine treatment (8.20) and 24-hours pre-ibogaine treatment (7.64) to 24-hours post-ibogaine treatment (5.26) and 48-hours post-ibogaine treatment (3.30) ($p < .01$). **Withdrawal – Self-rated (SOWS)**: Mean group scores decreased from 48-hours pre-ibogaine treatment (20.51) and 24-hours pre-ibogaine treatment (17.09) to 24-hours post-ibogaine treatment (12.63) and 48-hours post-ibogaine treatment (10.04) ($p < .01$). **Craving (Brief Self-control Scale)**: Mean group scores decreased from 48-hours pre-ibogaine treatment (6.58) and 24-hours pre-ibogaine treatment (5.98) to 24-hours post-ibogaine treatment (2.69) and 48-hours post-ibogaine treatment (1.92) ($p < .01$).

(*Continued*)

Table 1. (Continued).

Author (year) Country	Study Design	Sample Size (*n*=): Female (F), Male (M) Mean age (SD) Ethnicity: %	Substance of Dependence	Duration of Treatment and Intervention	Outcomes (Measures) and Time Points
Mash et al. (2018) West Indies	Case series	n = 191: 47F, 144 M n = 102 opioids dependency: 34F, 68 M 35.8 (9.9) White: 95.1% Hispanic: 2.9% Native American: 2.0% n = 89 cocaine dependency: 13F, 76 M 36.1 (9.1) White: 78.7% African American: 2.2% Hispanic: 15.7% Native American: 3.4%	Opioid or Cocaine	12-day inpatient treatment with Ibogaine HCl 8-12 mg/kg orally and motivational counseling during and post ibogaine	**Withdrawal – Clinician rated (OOWS)**: Scores decreased from pre-ibogaine dose (3–13) to~36-hours post-ibogaine dose (0–2) [†]. **Craving (Heroin Craving Questionnaire-29) (Opioid Dependent Participants)**: Emotionality (Negative Mood) mean scores decreased from baseline (3.51) to discharge (2.02) and 30-days follow-up (1.69) ($p < .001$). Purposefulness (Desire or intent to use drug now) mean scores decreased from baseline (4.10) to discharge (2.21) and 30-days follow-up (2.04) ($p < .001$). Compulsivity (Lack of confidence in ability to quit using drug) mean scores decreased from baseline (3.23) to discharge (2.04) and 30-days follow-up (1.64) ($p < .001$). Expectancy (Expected positive benefits of drug use) mean scores decreased from baseline (4.51) to discharge (3.74) and 30-days follow-up (2.90) ($p < .001$). **Craving (Cocaine Craving Questionnaire-45) (Cocaine Dependent Participants)**: Emotionality (Negative Mood) mean scores decreased from baseline (1.85) to discharge (1.09) and 30-days follow-up (1.19) ($p < .001$). Purposefulness (Desire or intent to use drug now) mean scores decreased from baseline (2.60) to discharge (1.54) and 30-days follow-up (1.57) ($p < .001$). Compulsivity (Lack of confidence in ability to quit using drug) mean scores decreased from baseline (4.27) to discharge (2.95) and 30-days follow-up (3.15) ($p < .001$). Expectancy (Expected positive benefits of drug use) mean scores decreased from baseline (2.51) to discharge (1.93) and 30-days follow-up (1.76) ($p < .001$). **Craving (Minnesota Cocaine Craving Scale)**: Craving Intensity mean scores decreased from baseline (5.51) to discharge (1.47) and 30-days follow-up (1.96) ($p < .001$). Craving Frequency mean scores decreased from baseline (2.28) to discharge (0.29) and 30-days follow-up (0.52) ($p < .001$). Craving Duration mean scores decreased from baseline (2.51) to discharge (1.36) and 30-days follow-up (1.21) ($p < .001$). **Depression (Beck Depression Inventory-II) (Opioid Dependent Participants)**: Mean scores decreased from baseline (16.5) to discharge (8.9) and 30-days follow-up (4.5) ($p < .001$). **Depression (Beck Depression Inventory-II) (Cocaine Dependent Participants)**: Mean scores decreased from baseline (14.3) to discharge (4.2) (1.0) and 30-days follow-up (4.5) ($p < .001$). **Mood (Profile of Mood Scale Depression Subscale) (Opioid Dependent Participants)**: Mean scores decreased from baseline (22.1) to discharge (10.8) and 30 days follow-up (5.8) ($p < .01$). **Mood (Profile of Mood Scale Depression Subscale) (Cocaine Dependent Participants)**: Mean scores decreased from baseline (19.4) to discharge (7.1) and 30-days follow-up (5.8) ($p < .001$). **Psychological Symptoms (Symptoms Checklist-90 Scale Depression Subscale) (Opioid Dependent Participants)**: Mean scores decreased from baseline (1.7) to discharge (0.8) and 30-days follow-up (0.4) ($p < .001$). **Psychological Symptoms (Symptoms Checklist-90 Scale Depression Subscale) (Cocaine Dependent Participants)**: Mean scores decreased total mean score from baseline (1.2) to discharge (0.5) and 30-days follow-up (0.3) ($p < .001$).

(*Continued*)

Table 1. (Continued).

Author (year) Country	Study Design	Sample Size (*n*=): Female (F), Male (M) Mean age (SD) Ethnicity: %	Substance of Dependence	Duration of Treatment and Intervention	Outcomes (Measures) and Time Points
					Qualitative (Subjective interpretations of experience within 3-days post ibogaine) (*n* = 60): • Useful for drug problems = 91.7% • Given insight into self-destructive behaviors = 86.7% • Mindful of need to become sober/abstinent now = 68.3% • Cleansed/healed/reborn = 50.0% • Second chance at life = 40.0% • Increased self-confidence = 33.3% • Impending self-destruction if drug use continued (saw images of their death) = 18.3% • Willingness to repeat ibogaine experience = 16.7%
Thomas et al. (2013)*; Argento et al. (2019)** Canada	Case series	n = 18, *n* = 12 in first retreat and *n* = 6 in second; data from *n* = 12 who attended both retreats and had no missing data 5F, 6 M (1 participant not accounted for) 38 (not specified) First Nations band (indigenous population in Canada)	Problematic substance use	4-day retreat Ayahuasca (tea) and group counseling	**Emotional Regulation (Difficulty in Emotional Regulation Scale)**: Analysis of Variance (ANOVA) scores improved from pre-treatment to 6-month follow-up. Exact values not provided ($p = .124$). **Mindfulness (Philadelphia Mindfulness Scale)**: ANOVA scores increased from pre-treatment to 6-month follow-up ($p = .041$) ††. **Empowerment (Empowerment Scale)**: ANOVA scores significantly increased from pre-treatment to 6-month follow-up ($p = .002$) ††. **Hope (Hope Scale)**: ANOVA scores significantly increased from pre-treatment to 6-month follow-up ($p = .023$) ††. **Quality of Life (McGill Quality of Life Questionnaire)**: Meaning and Outlook ANOVA scores increased from pre-treatment to 6-month follow-up for Meaning ($p = .005$) and Outlook ($p = .004$) scales. Psychological scale ANOVA scores increased from pre-treatment to 6-month follow-up ($p = .055$) ††. **Substance Use (4-Week Substance Use Scale) (Percentage of participants who had used)**: Tobacco use decreased from Baseline (81.8%) to 6-month follow-up (63.6%) ($n = 11$) †. Alcohol use decreased from Baseline (50%) to 6-month follow-up (20%) ($n = 10$) †. Cannabis use remained the same from Baseline (45.5%) to 6-month follow-up (45.5%) ($n = 11$) †. Cocaine use significantly decreased from Baseline (60%) to 6-month follow-up (0%) ($n = 10$) †. Sedative use remained the same from Baseline (18.2%) to 6-month follow-up (18.2%) ($n = 11$) †. Hallucinogen use increased from Baseline (0%) to 6-month follow-up (9.1%) ($n = 11$) †. Opioid use remained the same from Baseline (9.1%) to 6-month follow-up (9.1%) ($n = 11$) †. **Qualitative (Semi-structured interview at 6-month follow-up)**: **Connection with self**: overcoming fears and anger, finding love and respect for self, being given another chance **Connection with others**: Closer ties to family, enjoying time spent with others **Substance use**: Retreat helped release the hurt and pain from substance use, ayahuasca helped remove cravings for alcohol/crack cocaine

Key.
*: Denotes main paper of the study.
†*p* value for this comparison was not provided in the paper.
††Exact values for this comparison were not provided in the paper.
1SOWS: Subjective Opiate Withdrawal Scale.
2COWS: Clinical Opiate Withdrawal Scale.
3OOWS: Objective Opiate Withdrawal Scale.
**: Paper used for demographic data extraction only.

Psychedelic interventions

Three studies involved administration of solely a psychedelic substance with 97 participants; all examined ibogaine (including one using noribogaine) for opioid dependence (Brown and Alper 2018; Glue et al. 2016; Malcolm, Polanco, and Barsuglia 2018).

Remaining studies examined psychedelic-assisted psychotherapy with a total of 234 participants; one each examined psilocybin adjunct with motivational enhancement therapy (MET) for alcohol dependence (Bogenschutz et al. 2015), psilocybin adjunct with CBT for nicotine dependence (Johnson et al. 2014), ibogaine adjunct with motivational counseling for opioid and cocaine dependence (Mash et al. 2018), and ayahuasca adjunct with group counseling for problematic substance misuse (Thomas et al. 2013).

A total of 315 participants received at least one dose of a psychedelic intervention and nine received a placebo. All doses of psychedelics were administered orally except ayahuasca which was concocted in a tea.

Risk of bias

Four studies used a case series study design (Brown and Alper 2018; Malcolm, Polanco, and Barsuglia 2018; Mash et al. 2018; Thomas et al. 2013), two were before-and-after studies (Bogenschutz et al. 2015; Johnson et al. 2014), and one was a randomized controlled trial (RCT) (Glue et al. 2016). Only the RCT had a control group (placebo tablets). The risk of bias evaluation using the ICROMS tool is presented in Table 2. Many studies used sampling methods which may have introduced bias, threatening external validity. Sampling across studies found instances of self-referrals without further clinical assessment to ascertain fulfillment of eligibility criteria, as well as samples including participants who had already been through the intervention (Thomas et al. 2013). Although validated outcome measures were used, some were considerably subjective and lacked a method to independently verify the data. For example, two of three studies measuring abstinence lacked biological verification and utilized self-reported measures such as Time-Line Follow-Back (Bogenschutz et al. 2015) and the Addiction Severity Index Composite (Brown and Alper 2018). Additionally, a lack of blinding of participants and assessors might have introduced bias. Lack of control groups was not mitigated against when analyzing study findings and its implications were not discussed sufficiently. As most included studies used a before-and-after or case series, to evaluate treatment safety, tolerability, and feasibility, power calculations for detecting a pre-specified treatment effect were largely absent. Four studies included follow-up periods, which ranged from 1–57 months. Across the studies, many participants were lost to follow-up therefore not accounted for. Data available at post-intervention follow-up time points were limited and p values were not reported uniformly across studies.

Effects of psychedelic treatments on abstinence

Two studies measured abstinence (Brown and Alper 2018; Johnson et al. 2014). Only Johnson et al. (2014) provided biologically verified measures of abstinence. 50% of participants were reported as abstinent at 1-month follow-up in the ibogaine study for opioid dependence (Brown and Alper 2018) and 92% of nicotine-dependent smokers were reported as abstinent at 1-month following the first psilocybin session. Follow-ups began to show divergence between the studies, as 20% of opioid-dependent users were abstinent at 6-month follow-up, whereas 80% of nicotine-dependent smokers remained abstinent at 6-month follow-up. At 12-month follow-up, 20% participants receiving ibogaine reported abstinence from opioid and 67% of those receiving psilocybin sustained abstinence from nicotine (Brown and Alper 2018; Johnson, Garcia-Romeu, and Griffiths 2017).

Effects on substance use

All three studies that measured substance use reported statistically significant reductions in substance use measures. In one study which used psilocybin adjunct with MET to treat alcohol dependence (Bogenschutz et al. 2015), percentage of drinking days decreased from 42% at pre-treatment to 12% 1-month following the first psilocybin session. Percentage of heavy drinking days decreased from 35% at pre-treatment to 9% 1-month following the first psilocybin session. At 6-month follow-up, alcohol use showed significant reductions in percentage of drinking days and percentage of heavy drinking days as both reported 12% for each measure. In the psilocybin-assisted psychotherapy for nicotine dependence study (Johnson et al. 2014), 92% of participants were abstinent at 1-month follow-up hence substance use showed significant reduction. Of the 20% of participants who were not abstinent at 6-month follow-up, significant reductions were reported in the number of cigarettes smoked per day. Johnson, Garcia-Romeu, and Griffiths (2017) reported significantly reduced substance use at 12-month and longer follow-up. Thomas et al. (2013) reported significant reductions of

Table 2. Quality assessment of includes studies using ICROMS.

Study	Design	Aims & Justification	Sampling	Outcome Measures & Blinding	Follow-up	Other Study Aspects	Analytical Rigor	Other Considerations	ICROMS Minimum Score Required	Global Quality Score
Bogenschutz et al. (2015)	Before-and-after study	5	0	4	2	1	2	8	22	22
Brown and Alper (2018)	Case series	1	0	2	2	0	0	7	22	12
Glue et al. (2016)*	RCT	2	3	5	6	2	2	7	22	27
Johnson et al. (2014)*	Before-and-after study	5	2	2	1	0	1	7	22	18
Malcolm, Polanco, and Barsuglia (2018)	Case series	4	0	2	2	2	0	8	22	18
Mash et al. (2018)	Case series	2	0	2	2	1	2	7	22	16
Nielson et al. (2018)*	Qualitative study	4	2	1	2	1	1	6	16	17
Thomas et al. (2013)	Case series	4	0	2	2	1	2	6	22	17

problematic cocaine use at 6-month follow-up following the ayahuasca and group counseling treatment; however, those who misused cannabis and opioids did not show a decrease post-treatment.

Effects on psychosocial and mental health outcomes

Four studies reported effects on mental health and quality of life (Bogenschutz et al. 2015; Johnson et al. 2014; Mash et al. 2018; Thomas et al. 2013). Outcomes measuring mood using the Profile on Mood Scale (POMS) were administered in both the psilocybin-assisted therapy for alcohol dependence study and the ibogaine-assisted therapy for cocaine dependency or opioid dependency. POMS scores demonstrated statistically significant improvement in the *Vigor* subscale at 6-months follow-up from the beginning of treatment (Bogenschutz et al. 2015). POMS scores were not significant at any other time points. In the ibogaine-assisted therapy study, POMS scores demonstrated statistically significant improvement in the *Depression/Dejection* subscale following discharge from treatment as well as 30-days follow-up in both opioid dependent and cocaine-dependent participants (Mash et al. 2018).

Self-efficacy measured by the Alcohol Abstinence Self-Efficacy in the alcohol dependence study showed significant improvement at 2-month and 6-month follow-up relative to Baseline in the *Temptation* subscale. Significant improvement was also noted at 2-month and 9-month follow-up relative to 1-month follow-up in the *Confidence* subscale (Bogenschutz et al. 2015).

Statistically significant improvements were noted in the measures of empowerment using the Empowerment Scale, mindfulness using the Philadelphia Mindfulness Scale, hope using the Hope Scale, and quality of life – meaning and outlook using the McGill Quality of Life survey from pre-treatment to 6-month follow-up among participants in the ayahuasca-assisted psychotherapy study (Thomas et al. 2013).

Effects on craving

Four studies measured craving (Bogenschutz et al. 2015; Johnson et al. 2014; Malcolm, Polanco, and Barsuglia 2018; Mash et al. 2018).

Craving outcomes were measured 48 hours and 24 hours pre-ibogaine dose and at 24-hour and 48-hour post-ibogaine dose in the sole ibogaine therapy for opioid dependency using the Brief Substance Craving Scale (BSCS) (Malcolm, Polanco, and Barsuglia 2018). The BSCS demonstrated significant reduction in craving scores following ibogaine administration, but no follow-up data were reported. Craving was measured at baseline, discharge following ibogaine treatment, and at 1-month follow-up using the Heroin Craving Questionnaire (HCQ) for opioid-dependent participants and the Minnesota Cocaine Craving Scale and Cocaine Craving Questionnaire for the cocaine-dependent participants in the Mash et al. (2018) study. All three measures showed significant reductions in all subscales, sustained at 1-month follow-up.

The Questionnaire on Smoking Urges was used to measure craving in the psilocybin-assisted therapy for nicotine dependence study and the Penn Alcohol Craving Scale was used in the alcohol dependence study. Both psilocybin-assisted therapy studies reported significant reductions for alcohol and nicotine cravings at 6-month follow-up (Bogenschutz et al. 2015; Johnson et al. 2014).

Effects on withdrawal

Five studies measured withdrawal (Brown and Alper 2018; Glue et al. 2016; Johnson et al. 2014; Malcolm, Polanco, and Barsuglia 2018; Mash et al. 2018) of which three reported significant decreases (Brown and Alper 2018; Malcolm, Polanco, and Barsuglia 2018; Mash et al. 2018)

Withdrawal symptoms reported in the ibogaine study examining both opioid dependency and cocaine dependency measured by the Objective Opioid Withdrawal Scale showed decreases following treatment as well (Mash et al. 2018). Scores decreased from 0–13 pre-ibogaine dose to 0–2 post-dose measured approximately 24-hours after.

Withdrawal scores decreased post-treatment for the two studies which used sole-ibogaine intervention for opioids (Brown and Alper 2018; Malcolm, Polanco, and Barsuglia 2018). Both studies used validated outcome measures. The former study used the Subjective Opioid Withdrawal Scale (SOWS) taken one-hour prior to the first dose, and then given at varying intervals determined by the provider once no further dosing was required. The mean time between baseline and the second SOWS administration was 76.5 hours with a mean reduction of 17 points reported. The latter study used both the SOWS and Clinician Opioid Withdrawal Scale (COWS) administered 48 and 24-hours pre-ibogaine dose and 24 and 48-hours post-ibogaine dose. SOWS scores averaged 20.51 ± 13.66 and 17.09 ± 12.95 pre-ibogaine dose which decreased to 12.63 ± 11.95 and 10.04 ± 11.65 post-ibogaine dose. COWS scores averaged 8.2 ± 5.21 and 7.64 ± 5.27 pre-ibogaine dose followed by a decrease to 5.26 ± 4.31 and 3.30 ± 3.13 post-ibogaine dose.

Comparing SOWS scores in both studies, Brown and Alper (2018) reported a greater reduction in withdrawal symptoms than did Malcolm, Polanco, and Barsuglia (2018) (average of 17 vs 10.47). The difference may be explained by differences between the study designs and measurements. The Brown and Alper (2018) study administered the first test dose according to the weight of the participant, at 3 mg/kg. The Malcolm, Polanco, and Barsuglia (2018) study administered a total dose of 18-20 mg/kg with a standard dose of 100 mg to all participants and the remaining dose coming within 2-hours posttest dose. For example, a participant weighing 70 kg would have received 210 mg as an initial dose in the Brown and Alper (2018) study versus 100 mg in the Malcolm, Polanco, and Barsuglia (2018) study. Flood and booster doses were also administered at different times with flood dose (12 mg/kg) becoming available to participants in the Brown and Alper (2018) study 2–12 hours following initial dose and then a booster dose (3-5 mg) 1–16-hours post-flood dose. In the Malcolm, Polanco, and Barsuglia (2018) study, the flood dose was given within two hours of test-dose and booster doses (1-5 mg/kg) only administered if a participant experienced symptoms of withdrawal for the remainder of the program. The time between SOWS administration also differed, with Brown and Alper (2018) conducting follow-up an average of 28.5 hours later than Malcolm, Polanco, and Barsuglia (2018). The dosing, dosing schedules, and timing of outcome measurements may have influenced the results reported in these studies. Due to these differing designs, we are unable to draw any conclusions from the data.

Participants' experiences of psychedelic-assisted treatments

Qualitative data was synthesized from three studies: one examined ibogaine as an adjunct to motivational counseling for opioid and cocaine dependency (Mash et al. 2018), one was a qualitative report (Nielson et al. 2018) of the combined Psilocybin and MET intervention study for alcohol dependence (Bogenschutz et al. 2015), and Thomas et al. (2013) reported qualitative data on participants' experiences of ayahuasca-assisted therapy.

Common themes included psychedelic treatment being useful for substance misuse-related problems, being a tool for gaining insight, gaining self-confidence, and inducing mystical experiences. Participants described the psychedelic experience as helping them alleviate withdrawal symptoms and changing their relationship with the substance of dependency. Participants described an increase in self-confidence to abstain and change their substance use-related behaviors. Insight gained from the psychedelic experience, combined with the increased self-confidence, may have enabled substance-dependent participants to modify their maladaptive behaviors and adopt new positive coping mechanisms. Regarding mystical experiences, participants described a feeling of connection to a higher power. Participants associated the experience with an expanded sense of self-awareness with a higher power, and this connection helped remind them of their purpose.

There was divergence amongst some other themes. Participants receiving ibogaine often experienced visions from their past, characterized by autographical content that centered on early childhood experiences. In contrast, participants receiving psilocybin experienced euphoric states which resulted in improved mood (Nielson et al. 2018).

Meta-synthesis

Overall, the qualitative findings complement the quantitative findings in terms of effects on abstinence, reduction of substance misused, and related psychosocial effects. The qualitative synthesis provides context regarding the types of insights that were gained by participants and how their interpretations of the psychedelic treatment experience impacted their patterns of substance use and behaviors. Participants described the powerful and personal subjective effects of the psychedelic substance and reflected on it being a meaningful experience (Johnson et al. 2014; Thomas et al. 2013). For example, participants described improved relationships with family and developing closer bonds with them (Brown and Alper 2018; Thomas et al. 2013).

In the qualitative data, participants across different studies described mystical type experiences and this was hypothesized to influence treatment outcomes. Only two studies examining psilocybin (Bogenschutz et al. 2015; Johnson et al. 2014) attempted to quantify this aspect of the treatment. Studies examining ibogaine and ayahuasca did not attempt to quantify the acute psychoactive effects of the substance.

Discussion

The systematic review included one RCT, four case series studies, and two before-and-after studies to assess the effectiveness of psychedelic treatments for SUD and substance misuse. All studies were published within the past 10 years, which highlights the renewed and growing interest of this field. A total of 324 participants were included in the studies selected for review.

Overall, we identified insufficient evidence to support the effectiveness of psychedelic treatments for SUD and substance misuse. As few studies using a particular psychedelic for treating specific substance of abuse were found, no conclusions can be drawn on effects on specific SUDs. Notwithstanding this, we should bear in mind the diverse mechanisms of action of different treatment models using psychedelics on different SUDs. Although abstinence and substance use outcomes reported positive results over long-term timeframes, these were measured in only two and three of the studies, respectively. Effectiveness of psychedelic treatments on psychological and psychosocial outcomes remains inconclusive as well based on the available data derived from studies without a comparison group nor well-powered to establish treatment effects. Improvements across mood, depression, self-efficacy, and quality of life were reported for all psychedelic substances examined. Craving and withdrawal scores also demonstrate some improvement and may unveil underlying mechanisms of how this intervention may work.

A majority of participants across the studies encompass individuals who have had long-term substance misuse whereby multiple treatment modalities have been unsuccessful. Where there is data on abstinence and substance use available, potential benefits for psychedelic medicine in individuals who are unresponsive to standard treatments were found (Kuypers 2019). In healthy volunteers, psilocybin has been shown to increase positive attitudes, mood, social effects, and behavior (Griffiths et al. 2016), with a majority of participants rating the psychedelic experience as one of the most meaningful experiences of their lives (Griffiths et al. 2008). Mysticism is another component of the psychedelic experience that has been correlated with high ratings of personal meaning and spiritual significance at follow-up (Griffiths et al. 2008). A recent study using psilocybin-facilitated smoking addiction treatment (Garcia-Romeu, Griffiths, and Johnson 2014) found that smoking cessation outcomes being significantly correlated with measures of mystical experience on session days and retrospective ratings of personal meaning and spiritual significance of psilocybin sessions. Our results also identify a correlation between the "mystical state" induced by psychedelic treatment and the improvements seen in abstinence and substance use. This suggests a potential mediating role of mystical experience in psychedelic treatment.

Strengths and limitations

The strengths of the review include adherence to PRISMA guidelines. A protocol was published for transparency, reproducibility, and to reduce publication bias. This review incorporated a systematic and comprehensive search. To optimize identification and inclusion of ibogaine and ayahuasca studies more commonly examined in Latin American countries, we searched the LILACS database. Two independent researchers completed the study screening and quality assessment, thus minimizing errors and selection bias, and improving reliability and validity. Employing a mixed methods design enabled both quantitative and qualitative data to be included. This helped maximize the collection of all available data and allows integration of the effects of the intervention with people's perspective of experiencing the intervention.

This review has several limitations. Firstly, much of the research evidence was synthesized from studies of poor methodological quality or using designs not fit for effectiveness evaluation. Only one RCT was included, and only one study met the ICROMS minimum score for quality assessment. Considerable variation in the outcome measures also made interpretation of the results across studies challenging. As most studies examined the same group of participants pre-and post-psychedelic-assisted intervention, and did not include a comparison to standard care for SUD, no conclusions can be drawn for how psychedelic-assisted therapy outcomes compare to current treatments used for SUD. Furthermore, studies included commonly had significant loss of follow-up data, potentially leading to attrition bias and skewing the long-term findings. Although the systematic search was extensive, there is a possibility that not all studies were captured within this review.

Implications and recommendations

Our review findings suggest that the literature is still in preliminary stages, and further investigation is needed to support psychedelic-assisted treatments for substance-dependent individuals. The current lack of high-quality research may reflect feasibility challenges such as lack of funding in the area and legal restrictions for working with psychedelics (Nutt, King, and Nichols 2013; Sellers and Leiderman 2018). However, it is important for future research to comprise large-scale well-designed RCTs to assess the effectiveness of the psychedelic-assisted treatments for SUD or substance misuse, including psychedelics not identified in this review. Such RCTs should also directly compare the effectiveness of psychedelic-assisted treatments with

current treatment options for SUD (in addition to placebo) on measures such as craving, withdrawal, abstinence, and psychosocial and mental health outcomes. Building on the presented limitations, all studies should measure abstinence and substance use, including a measure of biological verification, and include longer-term follow-ups to establish long-term effectiveness. Examination of adverse effects should continue to further strengthen evidence of safety for supervised psychedelic-assisted treatments.

Future research should integrate qualitative data to elicit the mechanisms by which psychedelic-assisted treatments may affect individuals. Both quantitative and qualitative data should be collected at follow-ups. Qualitative data provides a voice to participants and can inform future guidelines and policy by ensuring that treatment is implemented in a way that is sensitive and inclusive of their needs.

Clinicians should be aware of the current evidence and be able to advise their patients of the scarce evidence of the low-quality studies and the ongoing trials in development. Psychedelics were often used as adjuncts to psychotherapies such as MET, CBT, and counseling. This demonstrates that psychological therapies which support individuals to understand their root issues, change behavior patterns, and learn adaptive coping mechanisms will likely remain beneficial for this population.

Conclusion

Research into psychedelic treatments for a variety of psychiatric disorders is underway in the 21st century. Our findings indicate that there is currently not enough evidence to suggest that psychedelic and psychedelic-assisted treatments are effective for SUD and substance misuse. Clinical improvements have been found in some of the research evidence, however, these findings are limited by their methodological design and research quality. Better understanding of effectiveness can be developed in future research by conducting large-scale RCTs, with inclusion of qualitative study designs, and long-term follow-ups.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Raman Sharma MSc http://orcid.org/0000-0002-5456-3461
Rachel Batchelor MSc http://orcid.org/0000-0002-0426-2388
Jacqueline Sin PhD http://orcid.org/0000-0003-0590-7165

References

Alcohol and Drug Foundation. 2019. Drug wheel. Accessed June 28, 2021. https://adf.org.au/insights/drug-wheel .

American Psychiatric Association. 2013. *Diagnostic and statistical manual of mental disorders*. 5th. Accessed June 28, 2021. 10.1176/appi.books.9780890425596.

Argento, E., R. Capler, G. Thomas, P. Lucas, and K. W. Tupper. 2019. A qualitative analysis of preliminary findings among an Indigenous community in Canada. *Drug and Alcohol Review* 38 (7):781–89. doi:10.1111/dar.12985.

Bogenschutz, M. P., A. A. Forcehimes, J. A. Pommy, C. E. Wilcox, P. C. R. Barbosa, and R. J. Strassman. 2015. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology* 29 (3):289–99. doi:10.1177/0269881114565144.

Brown, T. K., and K. Alper. 2018. Treatment of opioid use disorder with ibogaine: Detoxification and drug use outcomes. *The American Journal of Drug and Alcohol Abuse* 44 (1):24–36. doi:10.1080/00952990.2017.1320802.

Chesney, E., G. M. Goodwin, and S. Fazel. 2014. Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry* 13 (2):153–60. doi:10.1002/wps.20128.

Clarivate. 2021. Web of Science. Accessed June 28, 2021. https://clarivate.com/webofsciencegroup/solutions/web-of-science.

Cloutier-Gill, L., E. Wood, T. Millar, C. Ferris, and M. Eugenia Socias. 2016. Remission of severe opioid use disorder with ibogaine: A case report. *Journal of Psychoactive Drugs* 48 (3):214–17. doi:10.1080/02791072.2016.1180467.

Davis, A. K., E. Renn, A. M. Windham-Herman, M. Polanco, and J. P. Barsuglia. 2018. A mixed-method analysis of persisting effects associated with positive outcomes following ibogaine detoxification. *Journal of Psychoactive Drugs* 50 (4):287–97. doi:10.1080/02791072.2018.1487607.

Degenhardt, L., F. Charlson, A. Ferrari, D. Santomauro, H. Erskine, A. Mantilla-Herrara, H. Whiteford, J. Leung, M. Naghavi, M. Griswold, et al. 2018. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: A systematic analysis for the global burden of disease study 2016. *The Lancet Psychiatry* 5 (12):987–1012. doi:10.1016/S2215-0366(18)30337-7.

De Veen, B. T. H., A. F. A. Schellekens, M. M. M. Verheij, and J. R. Homberg. 2017. Psilocybin for treating substance use disorders? *Expert Review of Neurotherapeutics* 17 (2):203–12. doi:10.1080/14737175.2016.1220834.

di Leo, F. 1975. The use of psychedelics in psychotherapy. *Journal of Altered States of Consciousness* 2 (4):325–37.

DiVito, A. J., and R. F. Leger. 2020. Psychedelics as an emerging novel intervention in the treatment of substance use

disorder: A review. *Molecular Biology Reports* 47 (12):9791–99. doi:10.1007/s11033-020-06009-x.

dos Santos, R. G. 2013. Safety and side effects of ayahuasca in humans-an overview focusing on developmental toxicology. *Journal of Psychoactive Drugs* 45 (1):68–78. doi:10.1080/02791072.2013.763564.

dos Santos, R.G., J. C. Bouso, M. Á. Alcázar-Córcoles, and J. E. C. Hallak. 2018. Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: A systematic review of systematic reviews. *Expert Review of Clinical Pharmacology* 11 (9):889–902. doi:10.1080/17512433.2018.1511424.

Dos Santos, R. G., F. L. Osorio, J. A. S. Crippa, J. Riba, A. Zuardi, and J. E. C. Hallak. 2016. Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): A systematic review of clinical trials published in the last 25 years. *Therapeutic Advances in Psychopharmacology* 6 (3):193–213. doi:10.1177/2045125316638008.

Garcia-Romeu, A., R. R. Griffiths, and M. W. Johnson. 2014. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Current Drug Abuse Reviews* 7 (3):157–64. doi:10.2174/1874473708666150107121331.

Garcia-Romeu, A., B. Kersgaard, and P. H. Addy. 2016. Clinical applications of hallucinogens: A review. *Experimental and Clinical Psychopharmacology* 24 (4):229–68. doi:10.1037/pha0000084.

Glue, P., G. Cape, D. Tunnicliff, M. Lockhart, F. Lam, N. Hung, C. T. Hung, S. Harland, J. Devane, R. S. Crockett, et al. 2016. Ascending single-dose, double-blind, placebo-controlled safety study of noribogaine in opioid-dependent patients. *Clinical Pharmacology in Drug Development* 5 (6):460–68. doi:10.1002/cpdd.254.

Griffiths, R. R., M. W. Johnson, M. A. Carducci, A. Umbricht, W. A. Richards, B. D. Richards, M. P. Cosimano, and M. A. Klinedinst. 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology* 30 (12):1181–97. doi:10.1177/0269881116675513.

Griffiths, R. R., W. A. Richards, M. W. Johnson, U. D. McCann, and R. Jesse. 2008. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology* 22 (6):621–32. doi:10.1177/0269881108094300.

Joanna Briggs Institute. 2014. Methodology for JBI mixed methods systematic reviews. Accessed June 28, 2021. https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Mixed-Methods.pdf .

Johnson, M. W., A. Garcia-Romeu, M. P. Cosimano, and R. R. Griffiths. 2014. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology* 28 (11):983–92. doi:10.1177/0269881114548296.

Johnson, M. W., A. Garcia-Romeu, and R. R. Griffiths. 2017. Long-term follow-up of psilocybin-facilitated smoking cessation. *The American Journal of Drug and Alcohol Abuse* 43 (1):55–60. doi:10.3109/00952990.2016.1170135.

Kuypers, K. P. C. 2019. Psychedelic medicine: The biology underlying the persisting psychedelic effects. *Medical Hypotheses* 125:21–24. doi:10.1016/j.mehy.2019.02.029.

Lappan, S. N., A. W. Brown, and P. S. Hendricks. 2020. Dropout rates of in-person psychosocial substance use disorder treatments: A systematic review and meta-analysis. *Addiction* 115 (2):201–17. doi:10.1111/add.14793.

Lizarondo, L., C. Stern, J. Carrier, C. Godfrey, K. Rieger, S. Salmond, J. Apostolo, P. Kirkpatrick, and H. Loveday. 2020. Mixed methods systematic reviews (Chapter 8). In *JBI manual for evidence synthesis*, ed. E. Aromataris and Z. Munn, Accessed April 15, 2022. https://synthesismanual.jbi.global.

Lowe, H., N. Toyang, B. Steele, H. Valentine, J. Grant, A. Ali, W. Ngwa, and L. Gordon. 2021. The therapeutic potential of psilocybin. *Molecules* 26 (10):2948–81. doi:10.3390/molecules26102948.

Mačiulaitis, R., V. Kontrimavičiūtė, F. Bressolle, and V. Briedis. 2008. Ibogaine, an anti-addictive drug: Pharmacology and time to go further in development. A narrative review. *Human & Experimental Toxicology (0960-3271)* 27 (3):181. doi:10.1177/0960327107087802.

Malcolm, B. J., M. Polanco, and J. Barsuglia. 2018. Changes in withdrawal and craving scores in participants undergoing opioid detoxification utilizing ibogaine. *Journal of Psychoactive Drugs* 50 (3):256–65. doi:10.1080/02791072.2018.1447175.

Maremmani, A. G. I., P. P. Pani, L. Rovai, S. Bacciardi, and I. Maremmani. 2017. Toward the identification of a specific psychopathology of substance use disorders. *Frontiers in Psychiatry* 8 (68):1–11. doi:10.3389/fpsyt.2017.00068.

Mash, D. C., L. Duque, B. Page, and K. Allen-Ferdinand. 2018. Ibogaine detoxification transitions opioid and cocaine abusers between dependence and abstinence: Clinical observations and treatment outcomes. *Frontiers in Pharmacology* 9 (529):1–12. doi:10.3389/fphar.2018.00529.

Mertens, L. J., M. B. Wall, L. Roseman, L. Demetriou, D. J. Nutt, and R. L. Carhart-Harris. 2020. Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. *Journal of Psychopharmacology* 34 (2):167–80. doi:10.1177/0269881119895520.

National Institute for Health and Care Excellence (NICE). 2012. *Drug use disorders in adults – Quality standard [QS23]*. London: NICE.

Nielson, E. M., D. G. May, A. A. Forcehimes, and M. P. Bogenschutz. 2018. The psychedelic debriefing in alcohol dependence treatment: Illustrating key change phenomena through qualitative content analysis of clinical sessions. *Frontiers in Pharmacology* 9 (132):1–13. doi:10.3389/fphar.2018.00132.

Nutt, D. J., L. A. King, and D. E. Nichols. 2013. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Reviews Neuroscience* 14 (8):577–85. doi:10.1038/nrn3530.

Page, M. J., J. E. McKenzie, P. M. Bossuyt, I. Boutron, T. C. Hoffmann, C. D. Mulrow, L. Shamseer, J. M. Tetzlaff, E. A. Akl, S. E. Brennan, et al. 2021. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *British Medical Journal* 372 (71):1–9. doi:10.1136/bmj.n71.

Pasareanu, A. R., A. Ospal, J. K. Vederhus, Ø. Kristensen, and T. Clausen. 2015. Quality of life improved following in-patient substance use disorder treatment. *Health and Quality of Life Outcomes* 13 (1):1–8. doi:10.1186/s12955-015-0231-7.

Passie, T., J. H. Halpern, D. O. Stichtenoth, H. M. Emrich, and A. Hintzen. 2008. The pharmacology of lysergic acid diethylamide: A review. *CNS Neuroscience & Therapeutics* 14 (4):295–314. doi:10.1111/j.1755-5949.2008.00059.x.

Pisano, V. D., N. P. Putnam, H. M. Kramer, K. J. Franciotti, J. H. Halper, and S. C. Holden. 2017. The association of psychedelic use and opioid use disorders among illicit users in the United States. *Journal of Psychopharmacology* 31 (5):606–13. doi:10.1177/0269881117691453.

Sellers, E. M., and D. B. Leiderman. 2018. Psychedelic drugs as therapeutics: No illusions about the challenges. *Clinical Pharmacology & Therapeutics* 103 (4):561–64. doi:10.1002/cpt.776.

Sharma, R., and J. Sin. 2021. A mixed methods systematic review of contemporary psychedelic-associated treatments for substance use disorders and substance misuse. Accessed June 28, 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021232944.

Soler, J., M. Elices, A. Franquesa, S. Barker, P. Friedlander, A. Feilding, J. C. Pascual, and J. Riba. 2016. Exploring the therapeutic potential of ayahuasca: Acute intake increases mindfulness-related capacities. *Psychopharmacology* 233 (5):823–29. doi:10.1007/s00213-015-4162-0.

Taylor, W. J. 1971. History and pharmacology of psychedelic drugs. *International Journal of Clinical Pharmacology, Therapy & Toxicology* 5 (1):51–57.

Thomas, G., P. Lucas, N. R. Capler, K. W. Tupper, and G. Martin. 2013. Ayahuasca-assisted therapy for addiction: Results from a preliminary observational study in Canada. *Current Drug Abuse Reviews* 6 (1):30–42. doi:10.2174/15733998113099990003.

Whelan, P. J., and K. Remski. 2012. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *Journal of Neurosciences in Rural Practice* 3 (1):45–50. doi:10.4103/0976-3147.91934.

Winkelman, M. 2014. Psychedelics as medicines for substance abuse rehabilitation: Evaluating treatments with LSD, peyote, ibogaine, and ayahuasca. *Current Drug Abuse Review* 7 (2):101–16. doi:10.2174/1874473708666150107120011.

World Health Organization. 2019. ICD-10 Version:2019. Accessed June, 28 2021. https://icd.who.int/browse10/2019/en.

Zingg, W., E. Castro-Sanchez, F. V. Secci, R. Edwards, L. N. Drumright, N. Sevdalis, and A. H. Holmes. 2015. Innovative tools for quality assessment: Integrated quality criteria for review of multiple study designs (ICROMS). *Public Health (London)* 133:19–37. doi:10.1016/j.puhe.2015.10.012.

Appendix

Appendix A: Search Strategy used in EMBASE

Embase<1996 to 2021 Week 8>

(1) "substance use disorder."mp. or exp Substance-Related Disorders/192780
(2) cannabis dependence.mp. or exp cannabis addiction/10147
(3) alcohol dependence.mp. or exp alcoholism/87347
(4) opioid dependence.mp. or exp Opioid-Related Disorders/22746
(5) narcotic dependence.mp. or exp Opioid-Related Disorders/22402
(6) cocaine dependence.mp. or exp Cocaine-Related Disorders/13478
(7) tobacco dependence.mp. or exp Tobacco Use Disorder/0
(8) or/2-7 125,425
(9) 1 and 8123135
(10) psychedelic.mp. or exp Hallucinogens/71228
(11) hallucinogen×.mp.3314
(12) exp psilocybine/or psilocybin×.mp.1334
(13) ketamine.mp. or exp ketamine/37508
(14) ibogaine.mp. or exp ibogaine/582
(15) lysergic acid diethylamide.mp. or exp Lysergic Acid Diethylamide/4145
(16) ayahuasca.mp.439
(17) 10 or 11 or 12 or 13 or 14 or 15 or 16108029
(18) psychotherapy.mp. or exp Psychotherapy, Psychodynamic/or exp interpersonal psychotherapy/or exp Psychotherapy, Brief/or exp psychotherapy/208089
(19) exp Cognitive Therapy/or cognitive behavio?ral therap×.mp.61882
(20) exp behavior therapy/or behavio?r therap×.mp. or exp cognitive therapy/72901
(21) exp mindfulness meditation/or exp mindfulness/or mindfulness.mp.14140
(22) exp counseling/or counsel×.mp.214124
(23) talking therap×.mp.222
(24) 18 or 19 or 20 or 21 or 22 or 23410295
(25) psychedelic assisted psychotherapy.mp.33
(26) (psychedelic.mp. or exp Hallucinogens/or hallucinogen×.mp. or (exp psilocybine/or psilocybin×.mp.) or (ketamine.mp. or exp ketamine/) or (ibogaine.mp. or exp ibogaine/) or (lysergic acid diethylamide.mp. or exp Lysergic Acid Diethylamide/) or ayahuasca.mp.) adj1 (psychotherapy.mp. or exp Psychotherapy, Psychodynamic/or exp interpersonal psychotherapy/or exp Psychotherapy, Brief/or exp psychotherapy/or (exp Cognitive Therapy/or cognitive behavio?ral therap×.mp.) or (exp behavior therapy/or behavio?r therap×.mp. or exp cognitive therapy/) or (exp mindfulness meditation/or exp mindfulness/or mindfulness.mp.) or (exp counseling/or counsel×.mp.) or talking therap×.mp.)2952
(27) 25 or 262972
(28) 9 and (17 or 27)10163
(29) limit 28 to (human and english language and yr="2000 – 2021" and adult<18 to 64 years>)4349